Criteria Specification

ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.1.0

Affiliation: Monogenic Diabetes VCEP
Description : ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version
Version : 1.1.0
Pilot Rules Submitted : 4/21/2023
Release Notes :
Updated language in PP4: "...patients tested because of neonatal diabetes, PP4 can be applied if there has been negative testing for monogenic causes for neonatal diabetes (ABCC8, KCNJ11, INS [if there is no consanguinity] EIF2AK3 [if there is consanguinity])" to "For patients tested because of neonatal diabetes, PP4 can be applied if there has been negative testing for major monogenic causes for neonatal diabetes. These include ABCC8, KCNJ11, and INS. In consanguineous cases, EIF2AK3 should be tested as well."

Rules for GCK

Gene: GCK (HGNC:4195)
Preferred Transcript: NM_000162.5
HGNC Name: glucokinase
Disease: monogenic diabetes (MONDO:0015967) **Mode of Inheritance:** Autosomal dominant inheritance

Criteria & Strength Specifications

PVS1

Original ACMG Summary

Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease.
Caveats:
- Beware of genes where LOF is not a known disease mechanism (e.g. GFAP, MYH7).
- Use caution interpreting LOF variants at the extreme 3' end of a gene.
- Use caution with splice variants that are predicted to lead to exon skipping but leave the remainder of the protein intact.
- Use caution in the presence of multiple transcripts.

Very Strong

Use *GCK* PVS1 decision tree created based on PVS1 decision tree from ClinGen SVI group[1]

- Variants generating PTCs 3' of c.1198 (p.Asp400) of NM_000162.3, which includes the last 55 nucleotides of exon 9 and exon 10, are not expected to cause NMD[2]. The

α13 helix (p.444-456), located at the C-end of the protein, has a critical role in GCK conformational change upon glucose binding. Individuals with PTCs in exon 10 have a MODY phenotype. Therefore, a “very strong” level of evidence will be applied for PTCs in exon 10.

- “Exon skipping or “use of a cryptic splice site that preserves reading frame” and “Single to multi-exon deletion that preserves reading frame”
  - single exon deletions
    - deletion of exon 1 is in-frame but over 20 families with GCK-MODY phenotype and exon 1 deletion (some also have promoter deletions) --> PVS1
    - deletions of single **exons 2,3,6 and 7** cause frameshift --> **PVS1**
    - deletions or skipping of **exons 8 and 9** are in-frame and the proportion is >10 % (52 AA and 78 AA, respectively) --> **PVS1**
    - deletions or skipping of **exons 4 and 5** are in-frame and the proportion is <10 % (40 AA and 32 AA, respectively). Exon 4 (p.122-161) and exon 5 (p.162-193) contain each a part of the active site that binds glucose /p.151-180[3] according to Beck et al., Biochemistry 2013/ --> **PVS1**
    - deletion of exon 10 (47 AA) – There are a number of patients with a GCK-MODY phenotype with reported with missense, frameshift, PTC, splice acceptor, and stop loss variants in exon 10 --> **PVS1**
- Apply PVS1_Supporting to initiation codon variants given MDEP has only reviewed one variant and classified as VUS (c.3G>A, PVS1_Supporting + PM2_Supporting; one case submitted, dx.53 and no other info provided to lab). The next methionine is at codon 8 and there are no variants classified as pathogenic 5' of p.Met8.
- Per recommendations from the SVI, when RNA analysis demonstrates abnormal splicing from non-canonical splice site variants, apply PS3 instead of PVS1.

Modification Type: Gene-specific

Strong

Use *GCK* PVS1 decision tree.

Per the SVI standard PVS1 decision tree, apply PVS1_Strong to duplications ≥ 1 exon in size, contained completely within gene, proven not in tandem, reading frame presumed disrupted, and NMD predicted to occur.

Modification Type: Strength

Supporting

Use *GCK* PVS1 decision tree.

- Apply PVS1_Supporting to initiation codon variants given MDEP has only reviewed one variant and classified as VUS (c.3G>A, PVS1_Supporting + PM2_Supporting; one case submitted, dx.53 and no other info provided to lab). The next methionine is at codon 8 and there are no variants classified as pathogenic 5' of p.Met8.

- Per recommendations from the SVI, when RNA analysis demonstrates abnormal splicing from non-canonical splice site variants, apply PS3 instead of PVS1.

Modification Type: Strength

Instructions: Use GCK PVS1 decision tree.

PS1

Original ACMG Summary

Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.
Example: Val->Leu caused by either G>C or G>T in the same codon.
Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level.

Strong

No change

Modification Type: None

Supporting

PS1 may be used at a supporting level for canonical and non-canonical splicing variants when a different variant at the same nucleotide has been previously classified as pathogenic and the variant being assessed is predicted by SpliceAI to have a similar (SpliceAI score within 10% of the original variant) or greater deleterious impact.

Modification Type: Strength

PS2

Original ACMG Summary

De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.
Note: Confirmation of paternity only is insufficient. Egg donation, surrogate motherhood, errors in embryo transfer, etc. can contribute to non-maternity.

Very Strong

Use SVI-recommended point-based system with specifications for “Phenotype Consistency” per instructions.

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Modification Type: Gene-specific,Strength

Strong

Use SVI-recommended point-based system with specifications for “Phenotype Consistency” per instructions.

Modification Type: Gene-specific,Strength

Moderate

Use SVI-recommended point-based system with specifications for “Phenotype Consistency” per instructions.

Modification Type: Gene-specific,Strength

Supporting

Use SVI-recommended point-based system with specifications for “Phenotype Consistency” per instructions.

Modification Type: Gene-specific,Strength

Instructions: To obtain maximum points (“phenotype highly specific for gene”), patient must meet criteria for PP4. To obtain standard points (“phenotype consistent with gene but not highly specific”), the phenotype of the patient must include hyperglycemia or impaired fasting glucose, with no evidence of an autoimmune etiology of diabetes and/or absolute or near-absolute insulin deficiency. Exclusionary evidence of an autoimmune etiology of diabetes and/or absolute or near-absolute insulin deficiency includes the following: One or more positive diabetes autoantibodies (IA-2A, ZnT8A+, GAD) (Ref 15, 16, 17, 18). Very low or negative C-peptide, defined as either fasting or non-fasting random C-peptide (<200pmol/L or 0.6ng/mL) (Ref 13, 14) or urinary C-peptide/creatinine ratio <0.2 nmol/mmol (Ref 16, 17). We expect to see hyperglycemia at birth in an individual with GCK-MODY and therefore consider an individual unaffected if euglycemic in childhood or adulthood. Since individuals typically do not present with symptoms of diabetes, a statement that someone is “nondiabetic” is insufficient to consider a parent unaffected; fasting glucose must be tested and found to be within normal limits (<100 mg/dl = 5.5 mmol/L) or HbA1c <=5.5% (37 mmol/mol) since the GCK range was 5.6 - 7.6% (38 – 60 mmol/mol)(Ref 19). Presence of clinically significant diabetes complications in anyone with the variant is an exclusion.

PS3

Original ACMG Summary

Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.
Note: Functional studies that have been validated and shown to be reproducible and robust in a clinical diagnostic laboratory setting are considered the most well-established.

Strong

Applicable to non-canonical splice site variants that have RNA and in silico evidence of aberrant splicing.

Modification Type: Gene-specific,Strength

Moderate

See list of approved functional studies and guidelines for interpretation of data.

Modification Type: Gene-specific,Strength

Supporting

See list of approved functional studies and guidelines for interpretation of data (below).

Modification Type: Gene-specific,Strength

Instructions: Use GCK PS3 decision tree, which incorporates the relative activity index (RAI), relative stability index (RSI), and assays that measure the impact of variants on binding with GKRP and GKA. (Ref 5,6,7,12). For canonical splice site variants, do not use PS3 for RNA studies demonstrating abnormal splicing, since PVS1 will already be used at some level. To use PS3, functional study must have been performed on a transfected variant. If a study was performed on a cell line generated from a patient sample (and therefore contains the variant plus any other genomic variation the patient has) does not count as PS3.

PS4

Original ACMG Summary

The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls.
Note 1: Relative risk (RR) or odds ratio (OR), as obtained from case-control studies, is >5.0 and the confidence interval around the estimate of RR or OR does not include 1.0. See manuscript for detailed guidance.

Note 2: In instances of very rare variants where case-control studies may not reach statistical significance, the prior observation of the variant in multiple unrelated patients with the same phenotype, and its absence in controls, may be used as moderate level of evidence.

Strong

7 or more occurrences in unrelated individuals = Strong.

Modification Type: Gene-specific,Strength

Moderate

4-6 occurrences in unrelated individuals = Moderate.

Modification Type: Gene-specific,Strength

Instructions: Variant should meet PM2_Supporting in order to use PS4 at any level (careful review of gnomAD QC data may be necessary to assess whether variant is real or an artifact, especially if variant is in a polyC region). Phenotype of the patient must include diabetes, with evidence of an autoimmune etiology and/or absolute or near-absolute insulin deficiency considered as exclusionary: One or more positive diabetes autoantibodies (IA-2A, ZnT8A+, GAD) (Ref 15,16, 17, 18). Very low or negative C-peptide, defined as either fasting or non-fasting random C-peptide (<200pmol/L or 0.6ng/mL) (Ref 13, 14) or urinary C-peptide/creatinine ratio <0.2 nmol/mmol (Ref 16, 17)

PM1

Original ACMG Summary

Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation.

Moderate

Applicable for glucose- and ATP-binding sites (see attached chart).

Modification Type: Gene-specific

Instructions: See attached chart.

PM2

Original ACMG

Summary

Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.
Caveat: Population data for indels may be poorly called by next generation sequencing.

Supporting

gnomAD 2.1.1 Popmax FAF ≤ 1:333,000 (≤ 0.000003 or 0.0003%) in European Non-Finnish population AND ≤ 2 copies observed in ENF AND ≤ 1 copy in any other founder or non-founder population.

Modification Type: Gene-specific

Instructions: Recommend using as supporting level of evidence (PM2_Supporting) per ClinGen guidance. Per guidance from ClinGen/SVI, PM2_Supporting + PVS1 is sufficient evidence of a variant being likely pathogenic. We recommend investigating the genotype metrics in gnomAD for variants that have been flagged for having failed one or more quality parameters, as it is possible that some of these filtered variants are actually real. The number of filtered alleles can be counted to determine whether PM2_Supporting would be met even if they were genuine calls. If the filtered calls are sufficient in number to not meet PM2_Supporting, then we would not use it. Because it is also possible that these calls are false positives, we would not use filtered variants to support BA1 or BS1. Allele frequency cutoffs using gnomAD 2.1.1. If there is a Popmax Filtering AF for both exomes and genomes, use that with the higher denominator.

PM3

Original ACMG

Summary

For recessive disorders, detected in trans with a pathogenic variant
Note: This requires testing of parents (or offspring) to determine phase.

Very Strong

Use SVI-recommended point-based system.

Modification Type: Strength

Strong

Use SVI-recommended point-based system.

Modification Type: Strength

Moderate

Use SVI-recommended point-based system.

Modification Type: Strength

Supporting

Use SVI-recommended point-based system.

Modification Type: Strength

Instructions: Applicable for variants found in neonatal diabetes. Criterion can also be used to interpret the pathogenicity of a heterozygous variant (i.e., GCK-MODY) if the variant under assessment has also been identified in a patient with neonatal diabetes in the homozygous state or in trans with a P/LP variant or VUS).

PM4

Original ACMG Summary

Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants.

Moderate

For single amino acid deletions, use as supporting level of evidence.

Modification Type: Strength

Supporting

For single amino acid deletions/insertions, use as supporting level of evidence

Modification Type: Strength

PM5

Original ACMG Summary

Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.
Example: Arg156His is pathogenic; now you observe Arg156Cys.
Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level.

Strong

Applicable once two amino acid changes have been classified as pathogenic at the same amino acid residue.

Modification Type: Strength

Moderate

The novel amino acid change must have a Grantham distance greater than or equal to the previously classified pathogenic variant.

Modification Type: Strength

Supporting

Apply if the previously classified amino acid change is likely pathogenic (rather than pathogenic) or if the previously classified variant is pathogenic but has a greater Grantham distance.

Modification Type: Strength

PM6

Original ACMG Summary

Assumed de novo, but without confirmation of paternity and maternity.

Not Applicable

Comments: Subsumed in PS2.

PP1

Original ACMG Summary

Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.
Note: May be used as stronger evidence with increasing segregation data.

Strong

Use thresholds suggested by Jarvik and Browning[8]

- Single Family : ≤ 1/32 (5 meioses)
- >1 Family : ≤ 1/16 (4 meioses)

Modification General recommendation,Gene-specific

Type:

Moderate

Use thresholds suggested by Jarvik and Browning[8]

- Single Family : ≤ 1/16 (4 meioses)
- >1 Family : ≤ 1/8 (3 meioses)

Modification Type: General recommendation,Gene-specific

Supporting

Use thresholds suggested by Jarvik and Browning[8]

- Single Family : ≤ 1/8 (3 meioses)
- >1 Family : ≤ ¼ (2 meioses)

Modification Type: General recommendation,Gene-specific

Instructions: Variable penetrance and phenocopies complicate co-segregation studies. The presence of type 1 and type 2 diabetes phenocopies and significance of variants in unaffected individuals as defined above will need to be considered. We expect to see hyperglycemia at birth in an individual with GCK-MODY and therefore consider an individual unaffected if euglycemic in childhood or adulthood. Since individuals typically do not present with symptoms of diabetes, a statement that someone is “nondiabetic” is insufficient to classify a family member as unaffected; fasting glucose must be tested and found to be within normal limits (<100 mg/dl = 5.5 mmol/L) or HbA1c test <=5.5% since the GCK range was 5.6 - 7.6% (Ref13).
Presence of clinically significant diabetes complications in anyone with the variant is an exclusion.

PP2

Original ACMG Summary

Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.

Supporting

Apply to all missense variants in GCK. gnomAD missense constraint score for *GCK* is 3.07 (observed/expected= 0.5), which is significant.

Modification Type: Gene-specific

PP3

Original ACMG Summary

Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.).
Caveat: As many in silico algorithms use the same or very similar input for their predictions, each algorithm should not be counted as an independent criterion. PP3 can be used only once in any evaluation of a variant.

Supporting

Use REVEL score of ≥0.70 as supportive evidence of pathogenicity. We also support using SpliceAI to assess the predicted impact of non-canonical splicing variants and synonymous variants: apply PP3 when the predicted change is at least 0.2[9,10]

Modification Type: General recommendation

PP4

Original ACMG Summary

Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.

Moderate

HbA1C 5.6 – 7.6% (38-60 mmol/mol) (if given multiple results, use maximum value) AND Fasting glucose 5.5-8 mmol/L (100-144 mg/dL) AND presence of any of the following additional features:

- PP4 phenotype found in pediatric patient (prepubertal or <10 years) (incidentally) AND
  - Not treated with insulin AND antibody negative
  - OR treated with insulin, antibody negative, and detectable C-peptide (> 0.6ng/mL) after 3 years
- Multiple values (= persistent)—multiple levels (>=2 counts) or well-documented persistent impaired fasting glucose (IFG)
- OGTT with minimal increment <3 mmol/l (54 mg/dl)
- Antibody negative
- Macrosomia in normoglycemic offspring of hyperglycemic gestational parent
- Low birthweight in hyperglycemic offspring of hyperglycemic gestational parent.
- Three-generation, dominant family history of diabetes or hyperglycemia (in a family not used for PP1)

Modification Type: Gene-specific,Strength

Supporting

HbA1C 5.6 – 7.6% (38-60 mmol/mol) (if given multiple results, use maximum value) AND Fasting glucose 5.5-8 mmol/L (100-144 mg/dL)

Modification Type: Gene-specific

Instructions: Negative testing of other genes not necessary because phenotype is very specific. Sixty percent of patients with GCK-MODY phenotype will test positive. There is a small chance that patient has HNF1A- or HNF4A-MODY in the early stages of disease (can get info about likelihood from family history). About 1% of patients with GCK-MODY will have deletions or other variants (e.g., promoter) that are not identified via Sanger sequencing-consider testing via NGS or other technology. For patients tested because of neonatal diabetes, PP4 can be applied if there has been negative testing for major monogenic causes for neonatal diabetes. These include ABCC8, KCNJ11, and INS. In consanguineous cases, EIF2AK3 should be tested as well

PP5

Original ACMG Summary

Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.

Not Applicable

This criterion is not for use as recommended by the ClinGen Sequence Variant Interpretation VCEP Review Committee. PubMed : 29543229

BA1

Original ACMG Summary

Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes or Exome Aggregation Consortium.

Stand Alone

gnomAD 2.1.1 Popmax Filtering AF ≥ 1:10,000 (≥ 0.01% or 0.0001).

Modification Type: Gene-specific

Instructions: Allele frequency cutoffs using gnomAD 2.1.1. If there is a Popmax Filtering AF for both exomes and genomes, use that with the higher denominator.

BS1

Original ACMG Summary

Allele frequency is greater than expected for disorder.

Strong

gnomAD 2.1.1 Popmax Filtering AF ≥ 1:25,000 (0.004% or 0.00004).

Modification Type: Gene-specific

Instructions: Allele frequency cutoffs using gnomAD 2.1.1. If there is a Popmax Filtering AF for both exomes and genomes, use that with the higher denominator.

BS2

Original ACMG Summary

Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with full penetrance expected at an early age.

Strong

We expect to see hyperglycemia at birth in an individual with _GCK_-MODY and therefore consider an individual unaffected if euglycemic in childhood or adulthood. Since individuals typically do not present with symptoms of diabetes, evidence that someone is “nondiabetic” is insufficient; fasting glucose must be tested and found to be within normal limits (<100 mg/dl / 5.6 mmol/L).

Modification Type: Gene-specific

BS3

Original ACMG Summary

Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing.

Strong

Applicable to non-canonical splice site variants that have RNA and in silico evidence of normal splicing (see BP4).

Modification Gene-specific

Type:

Supporting

Use GCK PS3 decision tree, which incorporates the relative activity index (RAI), relative stability index (RSI) and assays that measure the impact of variants on binding with GKRP and GKA.

Evidence of no impact on function:

- Normal RAI (>0.5) + normal RSI (>0.5) + normal inhibition/activation with GKRP/GKA = BS3_Supporting
- Normal RAI (>0.5) + normal RSI (>0.5) but no studies investigating GKRP/GKA = Cannot use PS3 or BS3

Gloyn, et al. 2005 [5]; Beer, et al. 2012 [6]; Raimondo, et al. 2014 [7]; Gloyn, et al. (2004)[12].

Modification Type: Gene-specific

Instructions: To use BS3, functional study must have been performed on a transfected variant. If a study was performed on a cell line generated from a patient sample (and therefore contains the variant plus any other genomic variants the patient has) it cannot count as BS3.

BS4

Original ACMG Summary

Lack of segregation in affected members of a family.
Caveat: The presence of phenocopies for common phenotypes (i.e. cancer, epilepsy) can mimic lack of segregation among affected individuals. Also, families may have more than one pathogenic variant contributing to an autosomal dominant disorder, further confounding an apparent lack of segregation.

Strong

Applicable to family members without variant who meet PP4 criteria (HbA1C 5.6 – 7.6% (38-60 mmol/mol) (if given multiple results, use maximum value) AND Fasting glucose 5.5-8 mmol/L (100-144 mg/dL))

Modification Type: Gene-specific

BP1

Original ACMG Summary

Missense variant in a gene for which primarily truncating variants are known to cause

disease.

Not Applicable

BP2

Original ACMG Summary

Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.

Supporting

Also applicable when in cis or trans with a likely pathogenic variant.

Modification Type: General recommendation

BP3

Original ACMG Summary

In frame-deletions/insertions in a repetitive region without a known function.

Not Applicable

BP4

Original ACMG Summary

Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc)
Caveat: As many in silico algorithms use the same or very similar input for their predictions, each algorithm cannot be counted as an independent criterion. BP4 can be used only once in any evaluation of a variant.

Supporting

Use a REVEL score of ≤0.15 as supportive evidence of no predicted impact on the gene or gene product. We also support using SpliceAI to assess the predicted impact of non-canonical splicing variants and synonymous variants: apply BP4 when the predicted change is below 0.2[9],[10].

Modification Type: General recommendation

BP5

Original ACMG Summary

Variant found in a case with an alternate molecular basis for disease.

Supporting

A variant in another monogenic diabetes gene is P/LP.

Modification Type: General recommendation

BP6

Original ACMG Summary

Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation.

Not Applicable

This criterion is not for use as recommended by the ClinGen Sequence Variant Interpretation VCEP Review Committee. **PubMed : 29543229**

BP7

Original ACMG Summary

A synonymous variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.

Supporting

Apply BP7 when the predicted change from SpliceAI is below 0.2 AND phyloP100 way < 2.0.

Modification Type: Gene-specific

Rules for Combining Criteria

Pathogenic

1 Very Strong *(PVS1, PS2_Very Strong, PM3_Very Strong)* **AND ≥ 1 Strong** *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)*

1 Very Strong *(PVS1, PS2_Very Strong, PM3_Very Strong)* **AND ≥ 2 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)*

1 Very Strong *(PVS1, PS2_Very Strong, PM3_Very Strong)* **AND 1 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)* **AND 1 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting,*

PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)

1 Very Strong *(PVS1, PS2_Very Strong, PM3_Very Strong)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

≥ 2 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)*

1 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)* **AND ≥ 3 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)*

1 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)* **AND 2 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

1 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)* **AND 1 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)* **AND ≥ 4 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

Likely Pathogenic

1 Very Strong *(PVS1, PS2_Very Strong, PM3_Very Strong)* **AND 1 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)*

1 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)* **AND 1 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)*

1 Very Strong *(PVS1, PS2_Very Strong, PM3_Very Strong)* **AND ≥ 1 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

1 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)* **AND 2 Moderate** *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)*

1 Strong *(PVS1_Strong, PS1, PS2, PS3, PS4, PM3_Strong, PM5_Strong, PP1_Strong)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

≥ 3 Moderate *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)*

2 Moderate *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)* **AND ≥ 2 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

1 Moderate *(PS2_Moderate, PS3_Moderate, PS4_Moderate, PM1, PM3, PM4, PM5, PP1_Moderate, PP4_Moderate)* **AND ≥ 4 Supporting** *(PVS1_Supporting, PS1_Supporting, PS2_Supporting, PS3_Supporting, PM2_Supporting, PM3_Supporting, PM4_Supporting, PM5_Supporting, PP1, PP2, PP3, PP4)*

Benign

≥ 2 Strong *(BS1, BS2, BS3, BS4)*

1 Stand Alone *(BA1)*

Likely Benign

1 Strong *(BS1, BS2, BS3, BS4)* **AND 1 Supporting** *(BS3_Supporting, BP2, BP4, BP5, BP7)*

≥ 2 Supporting *(BS3_Supporting, BP2, BP4, BP5, BP7)*

Files & Images

GCK PS3/BS3 Decision Tree: Monogenic Diabetes Variant Curation Expert Panel GCK PS3 and BS3 Decision Tree

GCK PM1 Residues: Amino acid residues in GCK for application of PM1

GCK Points Table for PM3 : Points table for applying PM3 (in trans) criteria for GCK

PS2 De Novo Points Table: Points table for determining strength of PS2 for apparent de novo variants

GCK PVS1 Decision Tree: Decision tree for determining strength of PVS1 for GCK variants

References

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